Protocol Addendum J2T-DM-KGAA (2)

A Long-Term Study to Assess the Safety and Efficacy of Lebrikizumab in Patients with Moderate-to-Severe Atopic Dermatitis

NCT04392154

Approval Date: 14-Dec-2022

A LONG-TERM STUDY TO ASSESS THE SAFETY AND EFFICACY OF LEBRIKIZUMAB IN PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Protocol Number	**DRM06-AD07/J2T-DM-KGAA**
Protocol Final Date	**27 March 2020**
Study Drug	**Lebrikizumab (DRM06/LY3650150)**
IND Number	**119866**
EudraCT Number	**2020-001211-24**
Sponsor	**Dermira, Inc., a wholly owned subsidiary of Eli Lilly and Company** **Lilly Corporate Center** **Indianapolis Indiana, 46285** **USA**
Medical Monitor	PPD **Pharm D** **Medical Director** PPD
Document ID	**VV-CLIN-075087**

Approval Date: Protocol Amendment (2) Electronically Signed and Approved by Lilly on date provided below.

PROTOCOL AMENDMENT 2 (SUMMARY OF CHANGES)

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	*12-Dec-2020*
Original Protocol	*27-Mar-2020*

The table below summarizes new changes being introduced to Amendment 2. Minor corrections or additions may not be included.

Protocol Section	Description of Change	Rationale
Title Page	Updated Sponsor address and Sponsor Medical Director	Change in Sponsor address and Medical Director
Sponsor Signature Page	Change in Medical Director	Update
Protocol Synopsis	Updated as per the changes made to the sections in the main body	Clarification
Section 1.4. Rationale for Dose and Treatment Regimen	Corrected the age to <18 years	Correction
Section 3 Study Design and Section 5.3 Study Drug Assignment	Clarified when DRM06-AD18 participants receive blinded and open label study drug	Clarification
Section 5.4 Study Blinding	Clarified unblinded interim analysis regarding DRM06-AD18	Clarification
Section 6.1 Permitted and Prohibited Treatments and Procedures	Included live vaccines are not permitted during the trial	To clarify guidance on vaccine use
Section 8.2.4.2 Adverse Events of Special Interest (AESIs)	Deleted the time that the sponsor or designee should report the AESIs Included that additional data will be collected in eCRF Included that "the investigator or designee" may discuss discontinuation of study drug or dose changes	Clarification
Section 8.2.8 Infections and Opportunistic Infections	Included this section	To match information provided with site training
Section 8.2.9 Product Complaints	Included product complaints language	To match information provided with site training
Section 9.1.1 Populations Analyzed	Included details related to mITT population	Clarification to match SAP
Section 11 References	Included the reference Winthrop KL et al	Update

Section 12 Appendices: Appendix 1 Schedule of Visits and Procedures	Included footnote 11	Clarification
Section 12 Appendices: Appendix 3 Protocol Amendment History	Included amendment 1 summary of changes	Update
Throughout the document	Replaced SOA with Appendix 1	Correction

SPONSOR SIGNATURE PAGE

A LONG-TERM STUDY TO ASSESS THE SAFETY AND EFFICACY OF LEBRIKIZUMAB IN PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Protocol Number: **DRM06-AD07/J2T-DM-KGAA**

Protocol Final Date: **27 March 2020**

Amendment (1) Date: **12 December 2020**

The signature below constitutes approval of this protocol. I certify that I have the authority to approve this protocol on behalf of the Sponsor, Dermira, Inc. The study will be conducted in accordance with this protocol and all applicable laws, rules, and regulations and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP), regulations of the United States (US) Food and Drug Administration (FDA), and the ethical principles that have their origin in the Declaration of Helsinki.

Authorized by:

_____ _____

Sponsor Signature Date

PPD Pharm D

Medical Director

INVESTIGATOR SIGNATURE PAGE

A LONG-TERM STUDY TO ASSESS THE SAFETY AND EFFICACY OF LEBRIKIZUMAB IN PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Protocol Number:	**DRM06-AD07/J2T-DM-KGAA**
Protocol Final Date:	**27 March 2020**
Amendment (1) Date	**12 December 2020**

I have read this protocol, including the appendices, and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined herein, according to the ethical principles that have their origin in the Declaration of Helsinki, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines for Good Clinical Practice (GCP) and applicable laws, rules and regulatory requirement(s) including those of the United States (US) Food and Drug Administration (FDA).

I agree to obtain the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of the protocol and informed consent prior to the start of the study.

I agree to obtain formal written informed consent in accordance with applicable federal and local regulations and international guidelines from all patients prior to their entry into the study.

I have received and reviewed the Investigator's Brochure including the potential risks and side effects of the product and instructions for use.

I agree to report to the Sponsor any adverse events that occur during the study in accordance with the ICH GCP guideline and the protocol.

I agree to ensure that all associates, colleagues, and employees assisting me with the conduct of the study are informed of their responsibilities in meeting the above commitments and the commitments set forth in the Investigator's Agreement.

I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with the ICH GCP guideline, and federal and local requirements.

I understand that the study may be terminated, or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

_____ _____

Investigator's Signature Date

_____

Investigator's Name (print)

PROTOCOL SYNOPSIS

Title:	A Long-term Study to Assess the Safety and Efficacy of Lebrikizumab in Patients with Moderate-to-Severe Atopic Dermatitis
Protocol Number:	DRM06-AD07/J2T-DM-KGAA
Phase:	3
Number of Sites:	Approximately 200 sites in North America, the European Union and Asia/Pacific region.

Study Population:

Adolescent patients (≥12 to <18 years weighing ≥40 kg) and adults who completed the DRM06-AD04, DRM06-AD05, DRM06-AD06, DRM06-AD17 or DRM06-AD18 trial

Sample Size:

Approximately 900 patients may enroll in this long-term extension study.

Study Objectives:

To evaluate the long-term safety and efficacy of lebrikizumab in patients with moderate-to-severe atopic dermatitis (AD).

Duration of Patient Participation:

Maximum total participation: up to 110 weeks (100 weeks on study plus a 12-week follow up safety visit after the last injection of study drug at Week 98).

Study Treatment:

Lebrikizumab, 250 mg (2 mL injection of 125 mg/mL)

Study Design:

Patients who have completed participation in a Dermira- or Lilly-sponsored lebrikizumab study (parent study), DRM06-AD04, DRM06-AD05, DRM06-AD06, DRM06-AD17 or DRM06-AD18, will be offered the opportunity to enroll in this study. This 100-week study is designed to assess the long-term safety and efficacy of lebrikizumab for moderate-to-severe atopic dermatitis.

Patients will be considered enrolled once all baseline procedures have been completed and the investigator has determined that the patient meets the inclusion and exclusion criteria. Two treatment regimens will be assessed: 250 mg lebrikizumab, administered every 2 weeks (Q2W) and 250 mg lebrikizumab, administered every 4 weeks (Q4W). The regimen assigned to each patient will be based on the treatment received in the patient's respective parent trial.

For the monotherapy trials, DRM06-AD04 and DRM06-AD05:

- Patients who were re-randomized, in the Maintenance Phase, to either 250 mg lebrikizumab Q2W or 250 mg lebrikizumab Q4W will continue to receive the same active treatment regimen.
- Patients who were receiving placebo in the Maintenance Phase will receive a loading dose of 500 mg lebrikizumab at the time of enrollment (Baseline) and at Week 2 followed by 250 mg lebrikizumab Q2W.
- Patients who were moved to the Escape Arm will continue to receive open label 250 mg lebrikizumab Q2W.
- Treatment regimen assignment will remain blinded during the long-term extension study until unblinding (see Section below), except for patients from an escape arm, who will receive open-label study drug. Placebo injections will be utilized in order to maintain the blind and ensure that all patients receive the same number and frequency of injections regardless of treatment regimen assignment.

For the TCS Combination trial, DRM06-AD06:

- Patients receiving 250 mg lebrikizumab Q2W who achieve an IGA 0,1 or an Eczema Area and Severity Index (EASI) -75 response (≥EASI-75) at Week 16 will be randomly allocated to receive 250 mg lebrikizumab Q2W or 250 mg lebrikizumab Q4W, in a 2:1 fashion, Q2W:Q4W, respectively.
- Patients receiving 250 mg lebrikizumab Q2W who do not achieve an IGA 0,1 or an EASI-75 response (<EASI-75) at Week 16 will receive 250 mg lebrikizumab Q2W.
- Patients who were receiving placebo will receive a loading dose of 500 mg lebrikizumab at the time of enrollment (Baseline) and at Week 2 followed by 250 mg lebrikizumab Q2W.
- Patients who were receiving rescue treatment and were initially randomized to lebrikizumab will receive 250 mg lebrikizumab Q2W.
- Patients who were receiving rescue treatment and were initially randomized to placebo will receive a loading dose of 500 mg lebrikizumab at the time of enrollment (Baseline) and at Week 2 followed by 250 mg lebrikizumab Q2W.
- Treatment regimen assignment will remain blinded during the long-term extension study until unblinding (see Section below). Placebo injections will be utilized in order to maintain the blind and ensure that all patients receive the same number and frequency of injections regardless of treatment regimen assignment.

For the Adolescent Safety trial, DRM06-AD17:

- All patients will continue to receive open label 250 mg lebrikizumab Q2W.

For the Vaccine trial, DRM06-AD18:

- Patients receiving 250 mg lebrikizumab Q2W will continue to receive 250 mg lebrikizumab Q2W (blinded study drug at Baseline and Week 2, then open-label study drug beginning at Week 4).
- Patients who were receiving placebo will receive a loading dose of 500 mg lebrikizumab at the time of enrollment (Baseline) and at Week 2 followed by open-label 250 mg lebrikizumab Q2W.
- Treatment regimen assignment will remain blinded during the long-term extension study until unblinding (until DRM06-AD18 study unblinded). Placebo injections will be utilized in order to maintain the blind and ensure that all patients receive the same number and frequency of injections regardless of treatment regimen assignment.

Patients who are not already administering study drug at home will be instructed on self-administration and allowed to inject study drug at home.

Patients will return to the clinic at Weeks 2, 4, 16 and every 12 weeks thereafter, through Week 100, for safety and efficacy assessments. Patients not achieving an EASI-50 (from parent study baseline) by Week 16, maintaining an EASI-50 response, or not achieving clinical benefit based on PI discretion should be terminated from this study.

Efficacy will be assessed using the Investigator Global Assessment (IGA), EASI and Body Surface Area (BSA). Patients who have been completing daily pruritus and sleep-loss assessments and weekly Patient-Oriented Eczema Measure (POEM) assessments as part of their participation in the parent trial (DRM06-AD04, DRM06-AD05, DRM06-AD06, and DRM06-AD18), will continue to collect this information in the long-term extension study (See Appendix 1). Patients who participated in the DRM06-AD06 study will continue to collect daily topical corticosteroid (TCS) and topical calcineurin inhibitor (TCI) use.

Safety will be assessed by monitoring the collection of adverse events, serum chemistry, hematology and urinalysis laboratory testing, physical examination, and vital signs.

Serum samples will be collected for pharmacokinetic analysis and immunogenicity.

Patients completing this study or who early terminate will return to the clinic for a safety follow-up visit 12 weeks after the last study drug injection.

A patient is considered to have completed the study if he/she has completed all required phases of the study including the last visit as shown in the Schedule of Visits and Procedures.

The end of the study is defined as the date of the last visit of the last patient in the study shown in the Schedule of Visits and Procedures.

An unblinded interim analysis will be performed to support regulatory submissions. Additional interim analyses may also be performed for regulatory interactions, safety updates, and disclosures.
Primary Endpoint: Describe the proportion of patients discontinued from study treatment due to adverse events through the last treatment visit.

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ACRONYMS

Acronym	Term
AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-t}	AUC from 0 to time t
AUC_{inf}	AUC from 0 to infinity
AUC_{last}	AUC from time 0 to the last time with quantifiable concentration
BSA	body surface area
C	Celsius
C_{max}	maximum (or peak) serum concentration
CK	creatine kinase
CSR	clinical study report
DRM06-AD04	Also known as: J2T-DM-KGAB
DRM06-AD05	Also known as: J2T-DM-KGAC
DRM06-AD06	Also known as: J2T-DM-KGAD
DRM06-AD07	Also known as: J2T-DM-KGAA
DRM06-AD17	Also known as: J2T-DM-KGAE
DRM06-AD18	Also known as: J2T-MC-KGAK
DSMB	Data Safety Monitoring Board
EASI	Eczema Area and Severity Index
EASI-50	50% reduction in EASI from Baseline
EASI-75	75% reduction in EASI from Baseline
EASI-90	90% reduction in EASI from Baseline
eCRF	electronic case report form
FDA	Food and Drug Administration
FLG	Filaggrin
GCP	good clinical practice

Acronym	Term
GGT	gamma-glutamyl transferase
HBV	hepatitis B
HCV	hepatitis C
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IFN	Interferon
Ig	immunoglobin
IGA	Investigator Global Assessment
IL	Interleukin
IRB	institutional review board
ITT	intent-to-treat
LOR	Loricrin
MedDRA	Medical Dictionary for Regulatory Activities
nAB	neutralizing antibodies
NRS	numerical rating scale
PFS-NSD	pre-filled syringe with a pre-assembled needle safety device
PI	principal investigator
PK	Pharmacokinetics
POEM	Patient Oriented Eczema Measure
Q2W	every 2 weeks
Q4W	every 4 weeks
SAE	serious adverse event
SAS®	statistical analysis software
SC	Subcutaneous
SCORAD	SCORing Atopic Dermatitis
SCORAD-50	50% reduction in SCORAD from baseline to a given timepoint
SCORAD-75	75% reduction in SCORAD from baseline to a given timepoint
SOC	system organ class
TBL	total bilirubin level
TCI	topical calcineurin inhibitor

Acronym	Term
TCS	topical corticosteroid
TEAE	treatment-emergent adverse event
ULN	upper limits of normal
US/USA	United States
W	Week
WOCBP	women of childbearing potential

1. BACKGROUND

1.1. Atopic Dermatitis

Atopic dermatitis (AD) is a complex disease that is determined by genetic, environmental and immunologic factors (Werfel, 2016; Simon, 2019).

Genetic studies of AD (Auriemma, 2013; Bieber, 2012; Weidinger, 2018) have shown that genes encoding for cytokines involved in the regulation of the immune system (IL-4, IL-5, and IL-13), are strongly associated with the development of AD (He, 2003; Hummelshoj, 2003; Novak, 2002). In addition, variants of genes that encode for proteins involved in skin barrier function such as filaggrin (FLG) and loricrin (LOR) are also associated with AD (Van Bever, 2011). Since FLG plays a central role in skin barrier integrity, loss of function mutations of the FLG gene is considered a major contributor to the development of early childhood AD (Bieber, 2008; Tanei, 2009; Bieber, 2012; Flohr, 2013).

Reduced epithelial barrier function, which represents the first line of protection against the environment, is thought to lead to sensitization to environmental allergens, associated with elevated immunoglobulin E (IgE) (present in about 50% to 80% of all patients with AD, particularly in children [Werfel, 2016]) and consistent with the presence in the skin of Type 2 cytokines (IL-4, IL-5, IL-9, IL-13, IL-25, IL-31, IL-33, and thymic stromal lymphopoietin and inflammation. Type 2 cytokines increase epidermal thickening, sensitization, inflammation, pruritus and decrease the expression of antimicrobial peptides and the barrier proteins FLG, LOR, and involucrin. IL-13 in particular can reduce epithelial integrity and barrier function through downregulation of FLG, LOR, and involucrin (Kim, 2008) and can act on keratinocytes in the skin to downregulate their differentiation (Howell, 2008). IL-13 also induces T-cell chemoattractants that mediate T-cell infiltration into AD lesions (Purwar, 2006) and may also induce IL-5 expression and eosinophil infiltration through the induction of eosinophil chemoattractants (Esche, 2004). Increased expression of IL-13 has consistently been reported in AD skin lesions and is associated with disease severity (Choy, 2012; Hamid, 1996; Jeong, 2003; La Grutta, 2005; Neis, 2006; Suarez-Farinas, 2013; Tazawa, 2004). The ubiquitous presence of IL-13 in the skin of patients with AD supports the evaluation of anti-IL-13 therapies in patients with AD.

1.1.1. Epidemiology of Pediatric Atopic Dermatitis

AD is one of the most common chronic medical diseases—15–30% of children and 2–10% of adults are affected, and the prevalence appears to have increased over the past two to three decades (Williams, 2008), with some geographic variability. With respect to disease severity, about 67% of AD pediatric patients have mild disease, 14 to 26% have moderate disease and 2 to 7% have severe disease (Silverberg, 2017). Approximately 85% of all cases of AD begin before age 5, with up to 70% of children having spontaneous remission before adolescence (Bieber, 2008; Hua, 2014; Illi, 2004).

1.1.2. Clinical Manifestations

Clinically, AD is characterized by xerosis, erythematous crusted eruption (dermatosis), lichenification and intense pruritus (Bieber, 2008), which along with the distribution, chronicity and history of skin lesions, form the basis for making the diagnosis AD. Flares are frequently triggered by exposure to environmental factors, irritants, and allergens (Bieber, 2009). Several clinical patterns, with differing distributions of skin lesions in distinct age groups, have been noted (Weidinger, 2016; Weidinger, 2018).

The infantile stage (up to 2 years of age) is characterized by eczema that is usually localized to the face, scalp, and extensor aspects of the arms and legs. The lesions are characterized by pruritic, red, eczematous plaques, erythema, papules, vesicles, excoriations, oozing, and formation of crusts.

The adult stage (from puberty onwards) is less predictable. Affected patients may have had only a few outbreaks since infancy, or they may have had a chronic, relapsing course. Lesions frequently localize to the face and neck (head-and neck dermatitis), as well in the flexures of the elbows and knees, and a considerable portion of patients (around 30%) develop atopic hand eczema, which may interfere with workplace activities. Like affected children, adolescents and adults commonly have lichenification of the flexures and have facial dermatitis.

Patients with AD have a high disease burden and their quality of life is significantly affected. In one study, AD was shown to have a greater negative effect on patient mental health than diabetes and hypertension (Zuberbier, 2006). Patients with moderate-to-severe AD have a higher prevalence of social dysfunction and sleep impairment, which are directly related to the severity of the disease (Williams, 2008). Depression, anxiety, and social dysfunction not only affect patients with AD, but also affect their caregivers (Zuberbier, 2006). Compared with psoriasis, another common and debilitating skin disease, patients with AD have lower physical vitality, social functioning, role-emotional, and mental health scores (Kiebert, 2002).

1.1.3. Treatment for AD

The therapeutic approach to AD consists primarily of trigger avoidance, skin hydration with bathing, and use of moisturizers and anti-inflammatory therapies consisting predominantly of topical corticosteroids (TCS). In many patients, treatment with TCS provides some measure of symptomatic relief but does not always adequately control the disease. In those patients who have persistent moderate-to-severe disease not responding adequately to TCS, the step-up options include topical calcineurin inhibitors (TCIs), phototherapy, and immunosuppressive agents such as oral corticosteroids, cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. Among these, only cyclosporine is approved for treatment of moderate-to-severe AD (nationally licensed in many European countries, but not in the US), and its use is limited to patients ≥16 years for a maximum treatment period of 8 weeks. Recently, a clinically efficacious and relatively safe treatment, anti-IL-4R monoclonal antibody, dupilumab, was approved for the treatment of adult and adolescent patients with moderate-to-severe AD. Despite these treatments, AD remains a major societal burden and a significant unmet medical need.

1.2. Lebrikizumab

Lebrikizumab is a humanized monoclonal immunoglobulin (Ig) G4 antibody (huIgG4) with a mutation in the hinge region that increases stability. Lebrikizumab binds specifically to soluble human interleukin (IL)-13 with high affinity, and potently inhibits IL-13 signaling through the IL-4Rα/IL-13Rα1 complex. Because lebrikizumab binds to IL-13 in a non-receptor binding domain (i.e., a portion of the molecule not involved in binding to its receptor), antibody-bound IL-13 can still bind its receptor (IL-13Rα1), but the engaged receptor complex cannot be activated.

1.3. Study Rationale and Benefit-Risk Assessment

1.3.1. Scientific Rationale

The use of lebrikizumab for AD is supported by numerous preclinical studies demonstrating that AD is characterized by the increased expression of IL-13 in skin. Moreover, clinical trials (a Phase 2a study GS29250 [Section 1.3.1.1] and a Phase 2b study DRM06-AD01 [Section 1.3.1.3]) with lebrikizumab demonstrated significant clinical benefit in patients with AD. Additional detailed discussion of the lebrikizumab studies is provided in the lebrikizumab Investigator's Brochure.

1.3.1.1. Summary of Study GS29250 (TREBLE)

Study Design

TREBLE was a Phase 2, global, randomized, double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of lebrikizumab in adult patients (18–75 years of age) with persistent moderate to severe AD, inadequately controlled by TCS. The study consisted of 3 study periods: a run-in period (2 weeks), a treatment period (12 weeks), and a safety follow-up period (8 weeks). Patients applied emollient at least once daily and TCS of medium potency to all active skin lesions twice daily through the study. A total of 212 patients were randomized as follows: 53 to the lebrikizumab 250 mg, single dose group; 53 to the lebrikizumab 125 mg, single dose group; 52 to the lebrikizumab 125 mg Q4W group; and 54 to the placebo Q4W group.

Efficacy Results

- EASI-50 at Week 12 (primary endpoint) was achieved by patients treated with lebrikizumab 125 mg Q4W, with a treatment difference between this group and placebo) of 20.1% p = 0.0261).

- Lebrikizumab 125 mg Q4W group demonstrated statistically significant differences from placebo in EASI-75 and SCORing Atopic Dermatitis-50 (SCORAD-50) and adjusted mean change from baseline to Week 12.

Safety Results

- Injection-site reactions occurred infrequently (1.3% all lebrikizumab treated vs. 1.9% placebo); all events were non-serious, lasted a median of 1 to 3 days, and did not lead to treatment discontinuation or interruption.

- Herpes viral infections and zoster occurred infrequently, but only among lebrikizumab-treated patients (6 of 156 [3.8%]); all events were non-serious, and none led to treatment discontinuation or dose interruption of lebrikizumab.

- Eosinophil-associated adverse events (AEs) were reported infrequently, but only occurred among lebrikizumab-treated patients (3.2%); however, all events were non-serious, did not result in interruption of treatment, and there were no other associated clinical symptoms noted.

- Allergic conjunctivitis events were only reported in lebrikizumab-treated patients (8 of 156 patients [5.1%] vs. 0% in placebo treated patients); all events were non-serious, did not lead to treatment discontinuation, all events recovered or resolved, and all patients had a history of asthma. Imbalances in allergic conjunctivitis events were not reported in previous lebrikizumab trials.

- The overall incidence of skin infection (noted in the system organ class [SOC] of infections and infestations) was 9.6% in all lebrikizumab arms combined, compared to 22% in the placebo arm.

Conclusions

The results of this trial suggested that lebrikizumab (on a background of mandatory twice daily TCS treatment) provided some treatment benefit, as measured through EASI and SCORAD, but also suggested that higher lebrikizumab dosing might provide greater clinical benefit. In addition, lebrikizumab was well tolerated with a safety profile generally consistent with that observed in previous trials conducted in other indications.

1.3.1.2. Summary of Study GS29735 (ARBAN)

Study Design

ARBAN was a Phase 2, randomized, open-label study designed to evaluate the safety and efficacy of lebrikizumab monotherapy in adult patients (18–75 years of age) with persistent moderate to severe AD, who were inadequately controlled by TCS. A total of 55 patients were randomized to treatment: 28 to lebrikizumab 125 mg Q4W and 27 to TCS.

Efficacy Results

- EASI-50 was achieved by 53.6% and 51.9% of patients in the lebrikizumab and TCS groups, respectively, with a treatment difference of 1.7%. EASI-75 was achieved by 39.3% and 37.0% of patients in the 2 groups, respectively, with a treatment difference of 2.3%.

- IGA scores of 0 or 1 were observed for 7.1% of patients in the lebrikizumab group and 25.9% of patients in the TCS group, giving a treatment difference of −18.8% (95% CI: −37.9%, 0.3%).

- The percent of patients achieving SCORAD-50 or SCORAD-75 showed treatment differences of −19.3% and −7.5%, respectively.

Safety Results

- AEs were reported for a higher proportion of patients in the lebrikizumab group compared with the TCS group (64.3% vs. 37.0%); a higher proportion of patients in the lebrikizumab group, compared with the TCS group, had an AE in the SOC of infections and infestations (42.9% vs. 25.9%). Upper respiratory tract infections were more common in the lebrikizumab group (14.3% vs. 3.7%).

- The overall incidence of skin infection (in the SOC of infections and infestations) was 17.9% in the lebrikizumab group and 7.4% in the placebo/TCS group.

- No serious AEs (SAEs), deaths, anaphylaxis, malignancy, protocol-defined parasitic or targeted intracellular infections of interest, herpes viral infections or zoster, or eosinophilia-associated AEs were reported.

Conclusions

Lebrikizumab was well tolerated at the dose of 125 mg Q4W; the safety profile was generally consistent with previous experience with lebrikizumab in previous trials.

1.3.1.3. Summary of Dose Ranging Study DRM06-AD01

Study Design

DRM06-AD01 was a Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the safety and efficacy of lebrikizumab in adult patients with moderate to severe AD. A total of 280 patients were randomized to 1 of 4 treatment groups (in a 3:3:3:2 ratio): 73 to lebrikizumab 125 mg Q4W (with a loading dose of 250 mg); 80 to lebrikizumab 250 mg administered every 4 weeks (Q4W) (with a loading dose of 500 mg); 75 to lebrikizumab 250 mg administered every 2 weeks (Q2W) (with a loading dose of 500 mg given at baseline and Week 2); 52 to placebo Q2W.

Efficacy Results

- Statistically significantly greater proportions of patients in each of the lebrikizumab 250 mg Q4W and 250 mg Q2W groups achieved EASI-50, EASI-75, or EASI-90 at Week 16 than the placebo group.

- A statistically significantly greater proportion of patients in each of the lebrikizumab 250 mg Q4W and 250 mg Q2W groups had both an IGA score of 0 or 1 and a ≥2-point improvement in IGA score at Week 16 than the placebo group.

- The lebrikizumab 250 mg Q2W group had a statistically significantly greater proportion of patients who achieved a ≥ 4-point improvement in pruritus numerical rating scale (NRS) compared with the placebo group.

- Positive changes in pruritus correlated with positive changes in sleep; the lebrikizumab 250 mg Q4W and 250 mg Q2W groups had statistically significant percent reductions in sleep loss due to itching compared with placebo (p=0.0459 and p=0.0062, respectively).

Safety Results

- The incidences of conjunctivitis (2.6% all lebrikizumab groups, 0 placebo), herpes infections (2.2% all lebrikizumab groups, 0 placebo), and herpes zoster (0.9% all lebrikizumab groups, 0 placebo) were relatively low.

- Four patients (1.8%) in the lebrikizumab groups and 2 patients (3.8%) in the placebo group had an SAE. Those reported in the lebrikizumab groups were

    - severe chest pain (1 patient in the 250 mg Q2W group)
    - severe hernial eventration (1 patient in the 125 mg Q4W group)
    - femur fracture of moderate severity (1 patient in the 125 mg Q4W group), and
    - panic attack of moderate severity (1 patient in the 250 mg Q2W group).

  Those reported in the placebo group were severe chronic obstructive pulmonary disease, severe edema peripheral, and severe pulmonary embolism. All SAEs were considered by the investigator as not related to study drug.

- Most AEs were considered not related to study drug; those considered related were reported for 16.2% of patients in the lebrikizumab groups and 5.8% of patients in the placebo group

Conclusions

This Phase 2b study showed that higher doses of lebrikizumab provided greater clinical benefit. All lebrikizumab doses induced statistically significant reductions in EASI scores compared to placebo, and a good dose response was observed for all primary and key secondary efficacy endpoints. The best response for all endpoints was observed with the highest lebrikizumab dose (250 mg Q2W), although the next highest dose (250 mg Q4W) also induced significant improvement in virtually all endpoints. All doses of lebrikizumab were well tolerated, without a dose response noted; AEs were generally mild or moderate and considered unrelated to study drug. These results provided the basis for dose selection for the pivotal Phase 3 studies.

1.3.1.4. Summary of DRM06-AD03 Phase 1 PK Study

Study Design

DRM06-AD03 was a Phase 1, randomized, parallel-group study to evaluate the pharmacokinetics (PK) and safety of lebrikizumab in healthy adult volunteers (18 to 45 years of age, inclusive). A total of 41 subjects were randomized as follows: 21 subjects received two 1-mL (125 mg) subcutaneous (SC) injections and 20 subjects received one 2-mL (250 mg) SC injection. The primary objective was to compare the PK (AUC, C_{max}) of the 2 lebrikizumab dosing regimens. Blood samples were collected prior to dosing and on Days 2, 4, 6, 8, 11, 15, 29, 43, 57, 71, 85 and 99 for PK and Day 29, 43, 57, 71, 85 and 99 for anti-drug antibodies (ADA).

Pharmacokinetic Results

For each AUC comparison (i.e., AUC_{last}, AUC_{inf}, and $AUC_{0\text{-}57d}$) geometric mean ratios were close to 1 with 90% CIs within the range of 80% to 125%, except for AUC_{inf}, which was just above the upper bound, with a value of 132%. The C_{max} geometric mean ratio was 0.89 with a 90% CI of 73%–108%.

Conclusions

Both the AUC and C_{max} results indicated similar overall exposure between the 2 lebrikizumab dosing regimens evaluated in this study, i.e., two 1-mL (125 mg) SC injections versus one 2-mL (250 mg) SC injection. Data from this study support the use of the 2-mL (250 mg) pre-filled syringe with a pre-assembled needle safety device (PFS-NSD) in the Phase 3 pivotal trials.

1.4. Rationale for Dose and Treatment Regimen

For the Phase 3 development program, a dosing regimen of 500 mg loading dose at baseline and Week 2, followed by 250 mg Q2W lebrikizumab was selected for study in the Induction Period (baseline to Week 16), based on an evaluation of safety, efficacy and PK data from the DRM06-AD01 and DRM06-AD03 trials (Sections 1.3.1.3 and 1.3.1.4). The DRM06-AD03 PK study conducted in healthy adults demonstrated that a single SC injection of 2-mL (250 mg) of lebrikizumab delivered comparable levels of lebrikizumab as did two 1-mL (125 mg) SC injections. This simulated the conditions under which study drug will be administered in Phase 3, further supporting the dose and treatment regimen for Phase 3 trials, lebrikizumab 250 mg Q2W with a loading dose of 500 mg given at Baseline and Week 2.

Following Induction, the Phase 3 development program will assess the long term safety and efficacy of both a 250 mg lebrikizumab Q2W dosing regimen and a 250 mg lebrikizumab Q4W dosing regimen in order to determine whether one or both regimens, one which involves less frequent dosing, might be effective in maintaining disease control over an extended period of time.

Adolescent Patients

In this Phase 3 study, adolescent patients (≥12 to <18 years weighing ≥40 kg), will be included and will receive the same doses of lebrikizumab described above for adults. The justification for this approach is as follows:

Both adults and adolescent patients have similar disease characteristics, typified by prominent Type 2 skin inflammation and similar clinical manifestations. In addition, both groups tend to have similar efficacy outcomes in response to therapies, including dupilumab (Simpson, 2018; Treister, 2019). Pharmacokinetic modeling and simulations of lebrikizumab dosing (population PK modeling of pooled data from 2259 adult asthma patients and a subsequent external posterior predictive check with lebrikizumab PK data from the DRM06-AD01 trial in adult AD patients) revealed similar kinetics for adults and adolescent patients, 12 to <18 years of age. The maximal exposures are predicted to be slightly (≤ 35%) higher in adolescent patients than in adults for any given dose due to the lower adolescent weight ranges and lebrikizumab exposure dependence on weight; however, the safety profile in adolescent patients, based on the exposure-response relationship analysis and on partial extrapolation, is comparable to that observed in adults.

1.5. Study Conduct Statement

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an independent review committee (IRB)/independent ethics committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs (and/or UADEs) or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objective

The objective of this study is to assess the long-term safety and efficacy of lebrikizumab in patients with moderate-to-severe AD.

2.2. Primary Endpoint

Describe the proportion of patients discontinued from study treatment due to adverse events through the last treatment visit.

2.3. Secondary Endpoints

Over the duration of the study:

- Proportion of patients with a response of IGA 0 or 1
- Proportion of patients achieving response of EASI-75 from baseline of parent study.

3. STUDY DESIGN

Patients who have completed participation in a Dermira- or Lilly-sponsored lebrikizumab study, DRM06-AD04, DRM06-AD05, DRM06-AD06, DRM06-AD17 or DRM06-AD18, will be offered the opportunity to enroll in this study. This 100-week study is designed to assess the long-term safety and efficacy of lebrikizumab for moderate-to-severe atopic dermatitis.

Patients will be considered enrolled once all baseline procedures have been completed and the investigator has determined that the patient meets the inclusion and exclusion criteria. Two treatment regimens will be assessed: 250 mg lebrikizumab, administered every 2 weeks (Q2W) and 250 mg lebrikizumab, administered every 4 weeks (Q4W). The regimen assigned to each patient will be based on the treatment received in the patient's respective parent trial.

For the monotherapy trials, DRM06-AD04 and DRM06-AD05:

- Patients who were re-randomized, in the Maintenance Phase, to either 250 mg lebrikizumab Q2W or 250 mg lebrikizumab Q4W will continue to receive the same active treatment regimen.

- Patients who were receiving placebo in the Maintenance Phase will receive a loading dose of 500 mg lebrikizumab at the time of enrollment (Baseline) and at Week 2 followed by 250 mg lebrikizumab Q2W.

- Patients who were moved to the Escape Arm will continue to receive open label 250 mg lebrikizumab Q2W.

- Treatment regimen assignment will remain blinded during the long-term extension study until unblinding (see Section below), except for patients from an escape arm, who will receive open-label study drug. Placebo injections will be utilized in order to maintain the blind and ensure that all patients receive the same number and frequency of injections regardless of treatment regimen assignment.

For the TCS Combination trial, DRM06-AD06:

- Patients receiving 250 mg lebrikizumab Q2W who achieve an IGA 0,1 or an EASI-75 response (≥EASI-75) at Week 16 will be randomly allocated to receive 250 mg lebrikizumab Q2W or 250 mg lebrikizumab Q4W, in a 2:1 fashion, Q2W:Q4W, respectively.

- Patients receiving 250 mg lebrikizumab Q2W who do not achieve an IGA 0,1 or an EASI-75 response (<EASI-75) at Week 16 will receive 250 mg lebrikizumab Q2W.

- Patients who were receiving placebo will receive a loading dose of 500 mg lebrikizumab at the time of enrollment (Baseline) and at Week 2 followed by 250 mg lebrikizumab Q2W.

- Patients who were receiving rescue treatment and were initially randomized to lebrikizumab will receive 250 mg lebrikizumab Q2W.

- Patients who were receiving rescue treatment and were initially randomized to placebo will receive a loading dose of 500 mg lebrikizumab at the time of enrollment (Baseline) and at Week 2 followed by 250 mg lebrikizumab Q2W.

- Treatment regimen assignment will remain blinded during the long-term extension study until unblinding (see Section below). Placebo injections will be utilized in order to maintain the blind and ensure that all patients receive the same number and frequency of injections regardless of treatment regimen assignment.

For the Adolescent Safety trial, DRM06-AD17:

- All patients will continue to receive open label 250 mg lebrikizumab Q2W.

For the Vaccine trial, DRM06-AD18:

- Patients receiving 250 mg lebrikizumab Q2W will continue to receive 250 mg lebrikizumab Q2W (blinded study drug at Baseline and Week 2, then open-label study drug beginning at Week 4).

- Patients who were receiving placebo will receive a blinded loading dose of 500 mg lebrikizumab at the time of enrollment (Baseline) and at Week 2 followed by open-label 250 mg lebrikizumab Q2W.

- Treatment regimen assignment will remain blinded during the long-term extension study until unblinding (until DRM06-AD18 study unblinded). Placebo injections will be utilized in order to maintain the blind and ensure that all patients receive the same number and frequency of injections regardless of treatment regimen assignment.

Patients who are not already administering study drug at home will be instructed on self-administration and allowed to inject study drug at home.

Patients will return to the clinic at Weeks 2, 4, 16 and every 12 weeks thereafter, through Week 100, for safety and efficacy assessments. Patients not achieving an EASI-50 (from parent study baseline) by Week 16, maintaining an EASI-50 response, or not achieving clinical benefit based on PI discretion should be terminated from this study.

Efficacy will be assessed using the Investigator Global Assessment (IGA), EASI and Body Surface Area (BSA). Patients who have been completing daily pruritus and sleep-loss assessments and weekly Patient-Oriented Eczema Measure (POEM) assessments as part of their participation in the parent trial (DRM06-AD04, DRM06-AD05, DRM06-AD06, and DRM06-AD18), will continue to collect this information in the long-term extension study (See Appendix 1). Patients who participated in the DRM06-AD06 study will continue to collect daily TCS/TCI use. Patients who participated in the DRM06-AD18 study will continue to be collected daily Skin Pain NRS.

Safety will be assessed by monitoring the collection of adverse events, serum chemistry, hematology and urinalysis laboratory testing, physical examination, pulse and blood pressure.

Serum samples will be collected for pharmacokinetic analysis and immunogenicity.

Patients completing this study or who early terminate will return to the clinic for a safety follow-up visit 12 weeks after the last study drug injection.

A patient is considered to have completed the study if he/she has completed all required phases of the study including the last visit as shown in the Schedule of Visits and Procedures.

The end of the study is defined as the date of the last visit of the last patient in the study shown in the Schedule of Visits and Procedures.

3.1. Duration of the Study

The maximum duration of a patient's participation in this study will be up to 110 weeks (100 weeks in study plus safety follow-up visit 12 weeks following the last injection of study drug at Week 98).

3.2. Study Population and Number of Patients

Approximately 900 patients, who have completed a prior lebrikizumab study, are expected to enroll in this study.

4. SELECTION OF PATIENTS

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1. Inclusion Criteria

Patients must meet all the following criteria to be eligible for this study:

1. Received treatment in a Dermira- or Lilly-sponsored lebrikizumab study, DRM06-AD04, DRM06-AD05, DRM06-AD06, DRM06-AD17 or DRM06-AD18 (parent trial) and have adequately completed the study treatments and last patient visit of the parent trial.

2. Willing and able to comply with all clinic visits and study-related procedures.

3. For women of childbearing potential: agree to remain abstinent (refrain from heterosexual intercourse) or use a highly effective contraceptive method during the treatment period and for at least 18 weeks after the last dose of lebrikizumab or placebo.

   NOTE: A woman of childbearing potential (WOCBP) is defined as a postmenarcheal female, who has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause) and has not undergone surgical sterilization (removal of ovaries and/or uterus).

   NOTE: The following are highly effective contraceptive methods: combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation, progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, bilateral tubal ligation, vasectomized partner, or sexual abstinence. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
   If the highly effective contraceptive methods are contraindicated or strictly declined by the patient, acceptable birth control methods may be considered. These may include a combination of the following methods:

   - male or female condom with spermicide and
   - cap, diaphragm, or sponge with spermicide.

4. Male patients are not required to use any contraception except in compliance with specific local government study requirements.

5. Provide signed informed consent/assent as described in Section 10.2.

4.2. Exclusion Criteria

Patients meeting any of the criteria below will not be included in this study:

1. Patients who, during their participation in the parent trial, developed a serious adverse event (SAE) deemed related to lebrikizumab, which in the opinion of the investigator or of the medical monitor could indicate that continued treatment with lebrikizumab may present an unreasonable risk for the patient. *
2. Patients who, during their participation in the parent trial, developed an AE that was deemed related to lebrikizumab and led to study treatment discontinuation, which in the opinion of the investigator or of the medical monitor could indicate that continued treatment with lebrikizumab may present an unreasonable risk for the patient. *
3. Conditions in the previous parent study consistent with protocol-defined criteria for permanent study drug discontinuation, if deemed related to lebrikizumab or led to investigator - or sponsor-initiated withdrawal of patient from the study (e.g., non-compliance, inability to complete study assessments, etc.). *
4. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study.

   * Note for exclusion criteria # 1, 2, and 3: In studies that are still blinded, conditions deemed related to the study treatment will be considered related to lebrikizumab.

5. STUDY DRUG

5.1. Investigational Medicinal Product

Lebrikizumab and placebo will be supplied to the investigator by the sponsor. Investigational product will be supplied as solution in a single use, sterile pre-filled syringe with a pre-assembled needle safety device (PFS-NSD), containing lebrikizumab or placebo. The 2-mL syringe of lebrikizumab is manufactured to contain 250 mg. Lebrikizumab cannot be distinguished visually from placebo.

5.2. Storage and Labeling

Study drug is to be stored under refrigerated conditions (2–8°C) and protected from excessive light and heat. Study drug should not be frozen, shaken or stored at room temperature. Temperature excursions outside of 2–8°C must be reported to the Sponsor or the designee. Clinical trial material will be labeled according to each country's regulatory requirements.

5.3. Study Drug Assignment

Assignment to treatment will be as follows:

For the monotherapy trials, DRM06-AD04 and DRM06-AD05:

- Patients who were re-randomized, in the Maintenance Phase, to either 250 mg lebrikizumab Q2W or 250 mg lebrikizumab Q4W will continue to receive the same active treatment regimen.
- Patients who were receiving placebo in the Maintenance Phase will receive a loading dose of 500 mg lebrikizumab at the time of enrollment (Baseline) and at Week 2 followed by 250 mg lebrikizumab Q2W.
- Patients who were moved to the Escape Arm will continue to receive open label 250 mg lebrikizumab Q2W.
- Treatment regimen assignment will remain blinded during the long-term extension study until unblinding (see Section below), except for patients from an escape arm, who will receive open-label study drug. Placebo injections will be utilized in order to maintain the blind and ensure that all patients receive the same number and frequency of injections regardless of treatment regimen assignment.

For the TCS Combination trial, DRM06-AD06:

- Patients receiving 250 mg lebrikizumab Q2W who achieve an IGA 0,1 or an EASI-75 response (≥EASI-75) at Week 16 will be randomly allocated to receive 250 mg lebrikizumab Q2W or 250 mg lebrikizumab Q4W, in a 2:1 fashion, Q2W:Q4W, respectively.

- Patients receiving 250 mg lebrikizumab Q2W who do not achieve an IGA 0,1 or an EASI-75 response (<EASI-75) at Week 16 will receive 250 mg lebrikizumab Q2W.

- Patients who were receiving placebo will receive a loading dose of 500 mg lebrikizumab at the time of enrollment (Baseline) and at Week 2 followed by 250 mg lebrikizumab Q2W.

- Patients who were receiving rescue treatment and were initially randomized to lebrikizumab will receive 250 mg lebrikizumab Q2W.

- Patients who were receiving rescue treatment and were initially randomized to placebo will receive a loading dose of 500 mg lebrikizumab at the time of enrollment (Baseline) and at Week 2 followed by 250 mg lebrikizumab Q2W.

- Treatment regimen assignment will remain blinded during the long-term extension study until unblinding (see Section below). Placebo injections will be utilized in order to maintain the blind and ensure that all patients receive the same number and frequency of injections regardless of treatment regimen assignment.

For the Adolescent Safety trial, DRM06-AD17:

- All patients will continue to receive open label 250 mg lebrikizumab Q2W.

For the Vaccine trial, DRM06-AD18:

- Patients receiving 250 mg lebrikizumab Q2W will continue to receive 250 mg lebrikizumab Q2W (blinded study drug at Baseline and Week 2, then open-label study drug beginning at Week 4).

- Patients who were receiving placebo will receive a loading dose of 500 mg lebrikizumab at the time of enrollment (Baseline) and at Week 2 followed by open-label 250 mg lebrikizumab Q2W.

- Treatment regimen assignment will remain blinded during the long-term extension study until unblinding (until DRM06-AD18 study unblinded). Placebo injections will be utilized in order to maintain the blind and ensure that all patients receive the same number and frequency of injections regardless of treatment regimen assignment.

For treatment assignments after unblinding, see Section below.

5.4. Study Blinding

For trials where blinding to treatment will be maintained, the Investigator, study-site personnel, and the patient will be blinded to treatment assignment until the unblinded interim analysis to support regulatory submissions occurs (or when DRM06-AD18 study is unblinded for DRM06-AD18 patients). The sponsor or designee could unblind a small team including but not limited to medical, statistics, data management, regulatory etc. to prepare for regulatory interactions, safety

updates, and disclosures if needed, while another team remains blinded to carry the day to day study work. After the interim database lock for the submission, patients will no longer receive placebo injections and will continue per assigned treatment group.

The integrity of the clinical study will be maintained by observing the treatment blind. If knowledge of a patient's treatment assignment is required for the patient's clinical care and/or safety, the Investigator should consult with the Sponsor's medical monitor prior to breaking the blind.

5.5. Study Drug Administration

Study drug will be administered to all patients in the clinic by designated and trained site staff from Baseline through the Week 4 visit and at all other scheduled clinic visits. Following the Week 4 visit, patients will be allowed to administer study drug at home. Sufficient study drug should be dispensed to cover at home administrations through the next study visit.

5.5.1. Instructions for Administration in the Clinic

Syringes should be at room temperature prior to injection (refer to the applicable Directions for Use provided by the sponsor).

5.5.2. Instructions for Administration at Home

Patients or caregivers will be instructed to self-administer study drug following the Week 4 visit.

Study site staff will instruct the patient or their caregiver on the proper injection technique and the patient or their caregiver will demonstrate for site staff proper injection technique prior to beginning at-home administration.

Instructions for use with details of the injection procedures, as well as storage and handling of syringes, will be provided to the participant and/or their caregiver to take home. Patients or caregivers who are not capable of administering study drug at home may continue to receive study drug injections in the clinic.

Patients will enter the details about at-home injections in the diary provided.

5.6. Study Drug Accountability

The Investigator must keep an accurate record of the number of cartons received, the study drug dispensed/used, and those returned to the Sponsor or designee. The Sponsor or designee will provide forms to facilitate inventory control. All study-drug accountability forms and treatment logs must be retained in the Investigator's permanent study file, and these records must be available for inspection at any time by the Sponsor, its designees, or by regulatory agencies.

The study monitor will perform drug accountability for all study drug at the site, and will assist in returning all empty, used syringe cartons, unused, and expired study drug, to the Sponsor/designees, or destroy it according to the study site's standard operating procedure, if accepted by the Sponsor.

6. CONCOMITANT MEDICATIONS AND PROCEDURES

All medications (including over-the-counter drugs, vitamins, and antacids) and over-the-counter emollient(s) taken/used at screening and throughout the study must be recorded. Patients should be instructed to consult with the Investigator prior to initiating any new medication (either self-administered non-prescription drugs or prescription therapy prescribed by another physician) while participating in the study. The Investigator is expected to examine the acceptability of all concomitant medications, topical preparations, and dietary supplements taken by patients participating in the trial.

- Medication entries should be specific to product name (if a combination drug product) and spelled correctly.
- The brand and specific product name for any over-the-counter emollient(s) should be noted and spelled correctly.
- Information on the dose, unit, frequency, route of administration, start date, discontinuation date, indication, and reason for use will be recorded.
- The use of any concomitant medication must relate to an AE listed on the AE electronic case report form (eCRF) or the patient's medical history unless it is a supplement or used as preventative care.

6.1. Permitted and Prohibited Treatments and Procedures

The use of concomitant medications for other medical conditions (e.g., hypertension, diabetes, acute infections) is permitted during this study. Inhaled corticosteroids and bronchodilators to control asthma are permitted.

Acute severe infections can be treated with systemic antibiotics, use of which must be recorded in the eCRF. However, chronic treatment with systemic antibiotics is not permitted.

Live or live attenuated vaccines are not permitted during the trial, but if taken, please contact sponsor or designee for additional guidance and hold study drug for 12 weeks post vaccination.

The use of a tanning booth/parlor is not permitted during the trial.

Planned or anticipated major medical procedures or surgeries should be avoided during the trial.

See Section 6.3 for details on approved AD medications and timing of use.

6.2. Moisturizers

Non-medicated moisturizers are to be used during the study. Patients may continue to use her/his current over-the-counter moisturizer regimen, if approved by the Investigator.

6.3. Treatments for AD

Intermittent use of topical rescue medications (e.g., TCS, TCIs and PDE4 inhibitors) for AD is permitted for the treatment of disease flares during the trial.

Patients coming from the TCS combination trial DRM06-AD06 and still on TCS use at the end of the parent study, may taper or stop TCS use, as needed. If AD lesions return or a patient experiences a flare, TCS treatment may be resumed at the patient's discretion. For patients coming from DRM06-AD06, TCS and TCI use will be recorded daily by the patient using an electronic diary, as indicated in the Schedule of Visits and Procedures (Appendix 1).

Patients who may require short-term systemic treatment for symptoms of AD will be assessed on a case-by-case basis and must be discussed with the Medical Monitor prior to initiating treatment.

The introduction of medications or therapies for other medical conditions known to affect AD (e.g., mycophenolate-mofetil, IFN-y, Janus kinase inhibitors, cyclosporine, azathioprine, methotrexate, phototherapy, or photochemotherapy) are not permitted during the study. Extended use of systemic corticosteroids for the treatment of AD are prohibited and require permanent discontinuation of Investigational Product. They may be used only for the treatment of an AE (for example, worsening of existing condition, such as asthma flare). If used for >30 days, sponsor approval is required for the patient to remain in the study.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. If the need for concomitant medication arises, the investigator should base decisions on the patient and clinical factors. Any additional medication (including the limited use of therapeutic agents which, if used under treatment regimens other than for treatment an AE or for appropriate medical management, might be considered therapies) whether prescription or over-the-counter, used at baseline and/or during the course of the study, must be documented with the start and stop dates.

Patients requiring long-term systemic treatment for symptoms of AD (e.g., non-responders) must be discontinued from the study.

Cannabinoid treatments for AD are prohibited. All medication used for AD must be recorded in the eCRF.

7. STUDY PROCEDURES

The required procedures for each study visit are outlined in Appendix 1. The timing of each study day is relative to the day of initial dosing (Day 1, Baseline).

7.1. Baseline Visit (Day 1)

Procedures for the Baseline Visit for study DRM06-AD07 are conducted as part of the study exit visit for the parent trial. Procedures are not duplicated but will be transferred electronically into the electronic data capture system where possible.

- Obtain written informed consent/assent prior to performing any study procedures
- Review Inclusion/Exclusion Criteria
- Measure vital signs
- Perform a complete physical examination
- Collect height and weight
- Review and record AEs
- Collect concomitant medication and procedure/therapy information
- Complete the following assessments: Investigator's Global Assessment (IGA), Body Surface Area (BSA), and Eczema Area and Severity Index (EASI)
- Confirm moisturizer use and review compliance report on the eDiary, remind patient to record the following as indicated in Appendix 1: Pruritus, Sleep-Loss and Skin Pain NRS (daily), TCS/TCI use (daily), and POEM (weekly)
- Draw blood samples for laboratory tests
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (WOCBP only)
- Instruct the patient to apply a moisturizer at least twice daily
- Draw a pre-dose blood sample for PK and anti-drug antibody (ADA) testing
- Administer study drug

7.2. Week 2 (± 3 Days)

- Complete the following assessments: IGA, BSA and EASI

- Measure vital signs
- Confirm moisturizer use and review compliance report on the eDiary, remind patient to record the following as indicated in Appendix 1: Pruritus, Sleep-Loss and Skin Pain NRS (daily), TCS/TCI use (daily), and POEM (weekly)
- Review and record AEs
- Collect concomitant medication and procedure/therapy information
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug

7.3. Week 4 (± 3 Days)

- Complete the following assessments: IGA, BSA and EASI
- Measure vital signs
- Confirm moisturizer use and review compliance report on the eDiary, remind patient to record the following as indicated in Appendix 1: Pruritus, Sleep-Loss and Skin Pain NRS (daily), TCS/TCI use (daily), and POEM (weekly)
- Review and record AEs
- Collect concomitant medication and procedure/therapy information
- Conduct urine pregnancy test (WOCBP only)
- Draw a pre-dose blood sample for PK and ADA testing
- Administer study drug
- Train the patient to self-administer study drug (if appropriate)
- Dispense study drug through next visit
- Remind patient to enter details about at home injections in the diary provided

7.4. Week 16 (± 5 Days)

- Complete the following assessments: IGA, BSA and EASI
- Measure vital signs
- Collect weight. In adolescents, also collect height

- Confirm moisturizer use and review compliance report on the eDiary, remind patient to record the following as indicated in Appendix 1: Pruritus, Sleep-Loss, and Skin Pain NRS (daily), TCS/TCI use (daily), and POEM (weekly)
- Review and record AEs
- Collect concomitant medication and procedure/therapy information
- Draw blood sample for hormones in adolescents
- Draw blood samples for laboratory tests
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug
- Review patient dosing diary and remind patient to enter details about at home injections in the diary provided
- Dispense study drug through next visit

7.5. Week 28 (± 5 Days)

- Complete the following assessments: IGA, BSA and EASI
- Measure vital signs
- Collect weight. In adolescents, also collect height
- Review and record AEs
- Confirm moisturizer use and review compliance report on the eDiary, remind patient to record the following as indicated in Appendix 1: Pruritus, Sleep-Loss and Skin Pain NRS (daily), TCS/TCI use (daily), and POEM (weekly)
- Collect concomitant medication and procedure/therapy information
- Draw blood sample for hormones in adolescents
- Draw blood samples for laboratory tests
- Conduct urine pregnancy test (WOCBP only)
- Draw a pre-dose blood sample for PK and ADA testing
- Administer study drug

- Dispense study drug through next visit
- Review patient dosing diary and remind patient to enter details about at home injections in the diary provided

7.6. Week 40 (± 5 Days)

- Complete the following assessments: IGA, BSA and EASI
- Measure vital signs
- Collect weight. In adolescents, also collect height
- Confirm moisturizer use and review compliance report on the eDiary, remind patient to record the following as indicated in Appendix 1: Pruritus, Sleep-Loss and Skin Pain NRS (daily), TCS/TCI use (daily), and POEM (weekly)
- Review and record AEs
- Collect concomitant medication and procedure/therapy information
- Draw blood sample for hormones in adolescents
- Draw blood samples for laboratory tests
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug
- Dispense study drug through next visit
- Review patient dosing diary and remind patient to enter details about at home injections in the diary provided

7.7. Week 52 (± 5 Days)

- Complete the following assessments: IGA, BSA and EASI
- Perform a complete physical examination, including weight. In adolescents, also collect height.
- Measure vital signs
- Review and record AEs

- Confirm moisturizer use, review compliance report on the eDiary, and collect the eDiary device.
- Collect concomitant medication and procedure/therapy information
- Draw blood samples for laboratory tests
- Draw a pre-dose blood sample for PK and anti-drug antibody (ADA) testing
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug
- Dispense study drug through next visit
- Review patient dosing diary and remind patient to enter details about at home injections in the diary provided

7.8. Week 64 (± 5 Days)

- Collect POEM (in office collection) for patients coming from Study DRM06-AD04, DRM06-AD05, DRM06-AD06 and DRM06-AD18
- Complete the following assessments: IGA, BSA, and EASI
- Measure vital signs
- Review and record AEs
- Collect concomitant medication and procedure/therapy information
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug
- Dispense study drug through next visit
- Review patient dosing diary and remind patient to enter details about at home injections in the diary provided

7.9. Week 76 (± 5 Days)

- Collect POEM (in office collection) for patients coming from Study DRM06-AD04, DRM06-AD05, DRM06-AD06 and DRM06-AD18
- Complete the following assessments: IGA, BSA, and EASI
- Collect weight. In adolescents, also collect height
- Measure vital signs
- Review and record AEs
- Collect concomitant medication and procedure/therapy information
- Draw blood samples for laboratory tests
- Draw a pre-dose blood sample for PK and anti-drug antibody (ADA) testing
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug
- Dispense study drug through next visit
- Review patient dosing diary and remind patient to enter details about at home injections in the diary provided

7.10. Week 88 (± 5 Days)

- Collect POEM (in office collection) for patients coming from Study DRM06-AD04, DRM06-AD05, DRM06-AD06 and DRM06-AD18
- Complete the following assessments: IGA, BSA, and EASI
- Measure vital signs
- Review and record AEs
- Collect concomitant medication and procedure/therapy information
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug

- Dispense study drug through next visit
- Review patient dosing diary and remind patient to enter details about at home injections in the diary provided

7.11. Week 100 / Early Termination (± 5 Days)

- Collect POEM (in office collection) for patients coming from Study DRM06-AD04, DRM06-AD05, DRM06-AD06 and DRM06-AD18
- Complete the following assessments: IGA, BSA, and EASI
- Perform a complete physical examination, including weight. In adolescents, also collect height
- Measure vital signs
- Review and record AEs
- Collect concomitant medication and procedure/therapy information
- Draw blood samples for laboratory tests
- Draw a blood sample for PK and anti-drug antibody (ADA) testing
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (WOCBP only)
- Review patient dosing diary.

7.12. Safety Follow-up (± 5 Days)

Patients who complete the study or terminate early from this study will return for safety follow-up visit 12 weeks after the last study drug injection.

- Update AEs and concomitant mediations and procedures that were ongoing at study termination
- Draw blood sample for PK and anti-drug antibody (ADA) testing

7.13. Unscheduled Visits

If an unscheduled visit is necessary, the following assessments should be included in the visit along with any assessments that are the reason for the visit (e.g., blood draw for a repeat of abnormal lab values):

- Review and record AEs and update concomitant medication and procedure/therapy information
- If the reason for the unscheduled visit is an exacerbation of atopic dermatitis, complete the following assessments: IGA, BSA and EASI

8. DETAILS OF ASSESSMENTS

8.1. Assessment of Efficacy

Each patient's AD will be assessed as specified in the Schedule of Visits and Procedures. Whenever possible, the same assessor should perform all assessments on a given patient.

8.1.1. Investigator Global Assessment (IGA)

The IGA is an instrument used to globally rate the severity of the patient's AD and is based on a 5-point scale ranging from 0 (clear) to 4 (severe). The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under morphological description be present. Assessors must be trained and certified by the Sponsor prior to conducting this assessment. The IGA must be conducted prior to conducting the EASI and BSA assessments.

8.1.2. Eczema Area and Severity Index (EASI)

The EASI is used to assess the severity and extent of AD; it is a composite index with scores ranging from 0 to 72, with the higher values indicating more severe and or extensive disease. A grade of 0 to 72 will be assessed by the Investigator or designee. Assessors must be trained and certified by the Sponsor prior to conducting this assessment.

8.1.3. Body Surface Area (BSA)

The BSA assessment estimates the extent of disease or skin involvement with respect to AD and is expressed as a percentage of total body surface. BSA will be determined by the Investigator or designee using the patient palm = 1% rule. Assessors must be trained and certified by the Sponsor prior to conducting this assessment.

8.1.4. Pruritus

Pruritus will continue to be assessed by all patients who evaluated pruritus as part of their parent trial participation using the same patient reported outcome instrument, the Pruritus Numerical Rating Scale (NRS). The Pruritus NRS is an 11-point scale used by patients to rate their worst itch severity over the past 24 hours with 0 indicating "No itch" and 10 indicating "Worst itch imaginable." Assessments will be recorded daily by the patient using an electronic diary through Week 52. Data will be transferred to the clinical database.

8.1.5. Sleep-Loss

Sleep-loss due to pruritus will continue to be assessed by all patients who evaluated sleep-loss as part of their parent trial participation using the same patient reported outcome instrument. Patients rate their sleep based on a 5-point Likert scale [0 (not at all) to 4 (unable to sleep at all)]. Assessments will be recorded daily by the patient using an electronic diary through Week 52. Data will be transferred to the clinical database.

8.1.6. Patient Oriented Eczema Measure (POEM)

POEM will continue to be assessed by all patients who completed a POEM assessment as part of their parent trial participation using the same patient reported outcome instrument. The POEM is a 7-item, validated, questionnaire used by the patient to assess disease symptoms over the last week. Patients are asked to respond to questions on skin dryness, itching, flaking, cracking, sleep loss, bleeding and weeping. All answers carry equal weight with a total possible score from 0 to 28 (answers scored as: No days=0; 1– 2 days = 1; 3-4 days = 2; 5–6 days = 3; everyday = 4). A high score is indicative of a poor quality of life. POEM responses will be captured using an electronic diary through Week 52, then captured at site visits starting at Week 64, and transferred into the clinical database.

8.1.7. Skin Pain Numeric Rating Scale (NRS)

Skin Pain NRS (Newton et al. 2019) is a patient-administered, validated, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "worst pain imaginable." Overall severity of a patient's skin pain is indicated by selecting the number that best describes the worst level of skin pain in the past 24 hours.

Skin Pain NRS will only be collected for patients continuing from DRM06-AD18. Participants will record the Skin Pain NRS assessments daily using an electronic diary at home through Week 52, as indicated in the Schedule of Visits and Procedures (Appendix 1).

8.2. ASSESSMENT OF SAFETY

8.2.1. Physical Examination

A complete physical examination will be conducted at baseline and at end-of-treatment and will cover general appearance, dermatological, head, ears, eyes, nose, throat, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, and lymphatic body systems. Height and weight will also be recorded.

At other study visits, a symptom-directed physical examination may be conducted at the discretion of the Investigator.

8.2.2. Vital Signs

Vital signs, including body temperature, respiratory rate (breath per minute), pulse (beats per minute), and blood pressure (mmHg), will be obtained with the patient in the seated position, after sitting for at least 5 minutes. Any abnormal findings which are new or worsened in severity and clinically significant, in the opinion of the Investigator, will be recorded as an AE. Vital sign measurements will be recorded in the eCRF.

8.2.3. Laboratory Evaluations

Laboratory tests will be analyzed using a central laboratory and include hematology with differential, serology, a standard chemistry panel (including liver-function tests), total cholesterol, standard urine testing, urine pregnancy test for women who are not post-menopausal

or surgically sterile and estradiol or testosterone testing in adolescents. Blood and urine will be collected from each patient as specified in the Schedule of Visits and Procedures or as clinically indicated. Any laboratory re-testing, if needed, should be conducted using the central laboratory. Laboratory data will be transferred to the clinical database.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and Appendix 1.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the clinically significant results will be reported as an AE in the AE section of the eCRF.

Blinding of laboratory test results
Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel.

Table 1: Laboratory Parameters

Hematology	Chemistry	Urine	Hormones	Serology
CBC with differential: Hematocrit Hemoglobin Red blood cells White blood cells Mean corpuscular hemoglobin MCH concentration Mean corpuscular volume RBC morphology Platelet count Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Sodium Potassium Chloride Calcium Phosphorus Bicarbonate Uric Acid Blood urea nitrogen Creatinine Total Protein Albumin Aspartate aminotransferase Alanine aminotransferase Lactic dehydrogenase Gamma-glutamyl transpeptidase Alkaline phosphatase Bilirubin (total and direct) Total cholesterol Non-fasting glucose	pH Specific gravity Protein Glucose Ketones Bilirubin Blood Nitrite Urobilinogen Leukocyte esterase At All Visits (WOCBP only): Urine beta human chorionic gonadotropin	Estradiol (adolescent females only)[a] Testosterone (adolescent males only)[a]	HBV DNA[b]

[a] Stop hormone tests when the patient reaches 18 years of age
b Only for participants who are anti-HBc reactive and anti-HBs nonreactive at parent study screening.

8.2.4. Adverse Events

AEs will be monitored throughout the study. Patients will be instructed to inform the Investigator and/or study staff of any AEs. At each visit, patients will be asked about AEs in a non-specific manner using open-ended questions so as not to bias the response (e.g., How have you been since the last visit?). Specific inquiry regarding reported AEs will be conducted when applicable. All AEs will be documented and recorded in the patient's eCRF.

Any patient who has an AE (serious or non-serious) will be evaluated by the Investigator and treated and followed until the symptom(s) return to normal or to clinically acceptable levels, as judged by the Investigator. A physician, either at clinical site, or at a nearby hospital emergency room, will administer treatment for any serious AEs (SAEs), if necessary. When appropriate, medical tests and examinations will be performed to document resolution of event(s).

8.2.4.1. Reporting

AEs that are ongoing at the exit visit of the parent trial will be carried over and followed. New AEs occurring from the time of consent to the end of study will be reported in the AE section of the eCRF. All AEs will be individually recorded in the eCRF. Any condition present prior to administration of study drug and that worsens after administration of study drug should be reported as an AE. Information regarding the onset, duration, severity, action taken, outcome, and relationship to study drug will be recorded.

New or worsening abnormal laboratory values and/or vital signs are to be recorded as AEs if they are considered to be of clinical significance by the Investigator or meet the criteria of an SAE as described in Section 8.2.4.3. Unless a diagnosis is available, signs and symptoms must be reported as individual AEs in the eCRF; a diagnosis is preferred.

The severity of an AE will be designated as mild, moderate or severe. The term “severe” is used to describe the intensity of an AE; the event itself, however, may be of relatively minor clinical significance (e.g., ‘severe’ upper respiratory infection). Severity is not the same as “serious”. Seriousness of AEs is based on the outcome/action of an AE. (Section 8.2.4.3)

The relationship of the AE to the study treatment should be determined by the Investigator and will be based on the following two definitions:

Not related: The AE is judged to not be associated with the study drug and is attributable to another cause.

Related: A causal relationship between the AE and the study drug is a reasonable possibility, i.e., there is evidence (e.g., dechallenge/rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment.

8.2.4.2. Adverse Events of Special Interest (AESIs)

The following treatment emergent adverse events are being designated adverse events of special interest (AESI):

- conjunctivitis
- herpes infection or zoster
- parasitic infection or an infection related to an intracellular pathogen

AESIs should be reported to the Sponsor or designee. Additional data will be collected for AESIs in the eCRF. Patient records must include any follow-up information regarding these AESIs.

Study drug should be discontinued if an adverse event is deemed persistent and if continuation of study drug would not be in the best interest of the patient. The investigator or designee may discuss discontinuation of study drug or dose changes with the Sponsor or designee prior to implementation.

8.2.4.3. Serious Adverse Events (SAEs)

An SAE is defined as any untoward medical occurrence that,

- Results in death
- Is in the opinion of the Investigator immediately life threatening (i.e., the patient is at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death)
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening, result in death, or require hospitalization, but based on appropriate medical judgment, it jeopardizes the patient, or may require medical or surgical intervention to prevent one of the outcomes listed. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The Investigator should institute any clinically necessary supplementary investigation of SAE information. In the case of patient death, any post-mortem findings/reports will be requested.

8.2.4.4. Reporting of SAEs

All SAEs, as defined in Section 8.2.4.3, regardless of causal relationship, must be reported to the Sponsor or designee within 24 hours of the Investigator becoming aware of the event. As soon as the Investigator becomes aware of an AE that meets the criteria for an SAE, the SAE should be documented to the extent that information is available.

SAEs will be recorded from the time of informed consent/assent until the end of the study. If, in the opinion of the Investigator, an SAE occurring outside the specified time window (i.e., following patient completion or terminations of the study) is deemed to be drug-related, the event should be reported with 24 hours.

SAEs must be recorded on an SAE form. The minimum information required for SAE reporting includes the identity of the Principal Investigator (PI), site number, patient number, event description, SAE term(s), reason why the event is considered serious (i.e., the seriousness criteria), and PI's assessment of the relationship of the event to study drug. Additional SAE

information including medications or other therapeutic measures used to treat the event, and the outcome/resolution of the event should also be recorded on the SAE form.

In all cases, the Investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. The Investigator may be required to provide supplementary information as requested by the Sponsor or its designee.

When reporting SAEs, the following additional points should be considered:

- Although signs, symptoms, and tests that support the diagnosis of an SAE should be provided, the Investigator should report the diagnosis or syndrome as the SAE term.

- Death should not be reported as an SAE, but as an outcome of a specific SAE (unless the event preceding the death is unknown). If an autopsy was performed, the autopsy report should be provided.

Although most hospitalizations necessitate reporting of an SAE, some hospitalizations do not:

- Hospitalization for elective or previously scheduled surgery, or for a procedure for a pre-existing condition that has not worsened after administration of study drug (e.g., a previously scheduled ventral hernia repair). SAEs must, however, be reported for any surgical or procedural complication that lead to prolongation of the hospitalization.

- Events that result in hospital stays for observation of <24 hours and that do not require a therapeutic intervention/treatment (e.g., an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics).

The Sponsor will process and evaluate all SAEs as soon as the reports are received. For each SAE received, the Sponsor will determine whether the criteria for expedited reporting to relevant regulatory authorities have been met.

The Sponsor will assess the likelihood that each SAE is related to study treatment, with the current Investigator's Brochure used as the reference document to assess expectedness of the event to study drug.

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file

it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

8.2.5. Pregnancy

The investigator should notify the Sponsor immediately regarding a pregnancy in a (1) female clinical trial patient or (2) female partner of a male clinical trial patient.

Pregnant female patients must be withdrawn from study drug.

If a female partner of a male patient becomes pregnant or suspects she is pregnant by the male patient, the male patient will be advised by the study Investigator to have his female pregnant partner inform her treating physician immediately.

The Investigator must perform medical assessments as clinically indicated and continue to follow the patient for ≥4 weeks after delivery. Medical details for both the mother and baby must be obtained.

The Investigator must complete a study-specific Pregnancy Form upon confirmation of a pregnancy. Pregnancy reporting forms will be provided to the site.

8.2.6. Hypersensitivity Reactions

Patients experiencing any hypersensitivity reaction should receive appropriate symptomatic medical care, as needed. Patients should be instructed to inform the site if a hypersensitivity reaction occurs. At the next study visit, a blood sample must be collected for immunogenicity analysis. The Sponsor or designee should be immediately consulted, particularly if the hypersensitivity reaction might be attributed to the study drug, and particularly if the reaction is severe, for discussions about discontinuing the study medication.

8.2.7. Hepatic Safety Monitoring

Close hepatic monitoring

The laboratory tests listed in Appendix 2, including ALT, AST, ALP,TBL, direct bilirubin, GGT, and CK should be repeated within 48 to 72 hours, to confirm the abnormality and to determine whether it is increasing or decreasing, if these conditions occur:

If a participant with baseline...	**has the following elevations:**
ALT or AST <1.5 times ULN	ALT or AST ≥3 times ULN
ALP <1.5 times ULN	ALP ≥2 times ULN
TBL <1.5 times ULN	TBL ≥2 times ULN
ALT or AST ≥1.5 times ULN	ALT or AST ≥2 times baseline
ALP ≥1.5 times ULN	ALP ≥2 times baseline
TBL ≥1.5 times ULN	TBL ≥1.5 times baseline (except for patients with Gilbert's syndrome)

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for the possible causes of the abnormal liver tests should be initiated by the investigator in consultation with the sponsor's designated medical monitor. At a minimum, this evaluation should include a physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking, and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of one to three times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if these conditions occur:

If a participant with baseline...	**has the following elevations:**
ALT or AST <1.5 times ULN	ALT or AST ≥3 times ULN with hepatic signs or symptoms*, or ALT or AST ≥5 times ULN
ALP <1.5 times ULN	ALP ≥3 times ULN
TBL <1.5 times ULN	TBL ≥2 times ULN
ALT or AST ≥1.5 times ULN	ALT or AST ≥2 times baseline with hepatic signs or symptoms*, or ALT or AST ≥3 times baseline
ALP ≥1.5 times ULN	ALP ≥2 times baseline
TBL ≥1.5 times ULN	TBL ≥2 times baseline, except for patients with Gilbert's syndrome

***Hepatic signs or symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, and/or rash.**

At a minimum, this evaluation should include a physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin-time/INR (PT-INR); viral hepatitis A, B, C, and E; tests for autoimmune hepatitis; and an abdominal imaging study, for example, ultrasound or CT scan.

Based on the participant's history and initial results, further testing should be considered in consultation with the sponsor's designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol.

Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist/gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

8.2.7.1. Additional Hepatic Data Collection in Participants Who have Abnormal Liver Tests during the Study

Additional hepatic safety data collection (hepatic safety eCRF) should be performed for participants who meet one or more of the following conditions:

- Elevation of serum ALT to ≥5 times ULN on two or more consecutive blood tests, if baseline ALT is <1.5 times ULN
    - In participants with baseline ALT ≥1.5 times ULN, the threshold is ALT ≥3 times baseline on two or more consecutive blood tests
- Elevation of TBL to ≥2 times ULN, if baseline TBL is <1.5 times ULN (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL ≥1.5 times ULN, the threshold should be TBL ≥2 times baseline
- Elevation of serum ALP to ≥2 times ULN on two or more consecutive blood tests, if baseline ALP <1.5 times ULN
    - In participants with baseline ALP ≥1.5 times ULN, the threshold is ALP ≥2 times baseline on two or more consecutive blood tests
- Hepatic event considered to be an SAE, and
- Discontinuation of study drug due to a hepatic event.

Note that the interval between the two consecutive blood tests should be at least 2 days.

8.2.7.2. Hepatitis B Testing and Monitoring

HBV DNA results that are reported as positive or as detecting HBV DNA, but HBV DNA is below the level of quantification: the sponsor's designated medical monitor should be contacted regarding the study status of the participant. HBV DNA testing is to be repeated as soon as is feasible. If HBV DNA is confirmed as positive, the participant must be permanently discontinued from study drug.

The participant is to be referred to, evaluated, and managed by a specialist physician with expertise in evaluation and management of viral hepatitis prior to discontinuation of any immunomodulatory and/or immunosuppressive therapy, including study drug. Timing of discontinuation from study drug relative to the initiation of any antiviral treatment for hepatitis is to be based on the recommendation of the consulting specialist physician, in conjunction with the investigator, and aligned with medical guidelines and standard of care.

8.2.7.3. Hepatitis C Testing and Monitoring

If HCV RNA is detected during the study, the study drug will be permanently discontinued and the participant should receive appropriate follow-up medical care.

8.2.8. Infections and Opportunistic Infections

Completion of the Infection eCRF is required for each infection (with the exception of the common cold) reported as an AE or SAE. The sponsor will identify infections considered to be opportunistic based on the article by Winthrop et al. (2015).

8.2.9. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges a deficiency related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a Lilly product after it is released for distribution. When the ability to use the product safely is impacted, the following are also considered as product complaints:

- deficiencies in labeling information, and
- use errors for device or combination products due to ergonomic design elements of the product.

Sponsor collects product complaints on investigational products and drug delivery systems used in clinical studies to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.
Complaints are also collected on comparators and other materials supplied, as required and instructed for the study.
Participants will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug or drug delivery system, so that the situation can be assessed.
Product complaints will be reported by the investigator to the sponsor per instructions provided on the study-specific Product Complaint Form.

All complaints associated with CT material and/or investigational device supplied by Lilly need to be reported within 24 hours of receipt of the complaint (see pharmacy manual). Updated product complaints information should be reported as soon as possible upon site awareness using the originally completed Product Complaint Form with all changes signed and dated by the investigator.

8.3. PK and ADA Sampling

Serum PK and ADA samples will be collected in all patients. Positive ADA results may be further evaluated for neutralizing antibodies. The procedural instructions will be provided in a separate PK and Serum Antibody Sampling manual.

8.4. Study Termination

The Sponsor has the right to terminate the study at any time. Should the study be terminated, the decision and reason will be communicated in writing by the Sponsor to the Investigator and request that all patients be discontinued. Patients should be scheduled for an Early Termination visit. The entire study will be stopped if:

- Evidence has emerged that, in the collective opinion of the Investigators at each site with the concurrence of the Sponsor, or the sole opinion of the Sponsor, continuation of the study is unnecessary or unethical
- The stated objectives of the study are achieved
- The Sponsor discontinues the development of the study drug

All data available for the patient at the time of study discontinuation must be recorded in the patient's records and the eCRF.

8.4.1. Early Termination of Study Patients

The Investigator will make reasonable efforts to keep each patient in the study. However, patients may terminate or be terminated early from the study for the following reasons:

- Voluntarily withdrawal of consent to participate in the study participation, at any time.
- Not achieving an EASI-50, from parent study baseline, by Week 16, maintaining an EASI-50 response, or not achieving clinical benefit based on PI discretion should be terminated from this study.
- Adverse event, laboratory abnormality or inter-current illness which, in the opinion of the Investigator, indicates that continued treatment and/or participation in the study is not in the best interest of the patient.
- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Patients requiring long-term systemic treatment for symptoms of AD (e.g., non-responders).
- Serious protocol violation, persistent non-compliance or requirement for medication or procedure prohibited by the protocol.
- Lost to follow-up
    - Two attempts of contact (e.g., telephone contact) followed by a certified letter of contact to the patient must be documented in a patient's study records for all patients who are believed to be lost to follow-up.

Patients who are terminated early from the study will have an Early Termination visit (Section 7.7) scheduled as soon as possible. All information, including the reason for early termination will be recorded in the patient's study records and in the eCRF.

8.4.2. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from the study unless there are extenuating circumstances that make it medically necessary for the participant to continue on study drug. If the investigator and the sponsor-designated medical monitor agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor designated medical monitor to allow the inadvertently enrolled participant to continue in the study.

8.4.3. Study Drug Discontinuation

8.4.3.1. Temporary Study Drug Discontinuation

Some possible reasons for temporarily withholding the study drug include, but are not limited to:

- HBV DNA results that are reported as positive, or as detecting HBV DNA, but HBV DNA is below the level of quantification: the sponsor's designated medical monitor should be contacted regarding study status of the participant. HBV DNA testing is to be repeated as soon as is feasible. If HBV DNA is confirmed as positive, the participant must be permanently discontinued from study drug.
- Hepatic event or liver test abnormality: the study drug should be withheld and additional testing performed following consultation with the Lilly-designated medical monitor, if the results of repeat tests following elevated ALT, ALP, or TBL include one of the following:
    - ALT ≥3 times ULN and TBL <2 times ULN
    - ALP ≥2 times ULN and TBL <2 times ULN
    - TBL ≥2 times ULN without increase from baseline in ALT or AST or ALP.

8.4.3.2. Permanent Study Drug Discontinuation

If HCV RNA is detected during the study, the study drug will be permanently discontinued, and the participant should receive appropriate follow-up medical care.

Study drug must be discontinued for patients who experience the following:

- Inter-current illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree
- Treatment-related AEs that are clinically significant, deemed persistent, in the judgment of the Investigator
- Unacceptable toxicity
- Pregnancy
- The participant develops any of the following conditions during the study:
    - **Malignancy**, except for successfully treated basal or squamous cell skin carcinoma
    - **Serious or opportunistic infection** that in the opinion of the investigator merits the study drug being discontinued. Such infections may include, but are not limited to:
        - HIV infection/acquired immune deficiency syndrome
        - active TB infection or untreated latent TB infection
        - HCV RNA positive
        - HBV DNA positive

NOTE: the HBV DNA result is to be confirmed if initial positive test result is positive but below the level of quantification. The participant is to be referred to, evaluated, and managed by a specialist physician with expertise in evaluation and management of viral hepatitis prior to discontinuation of any immunomodulatory and/or immunosuppressive therapy, including study drug. Timing of discontinuation from study drug relative to the initiation of any antiviral treatment for hepatitis is to be based on the recommendation of the consulting specialist physician, in conjunction with the investigator, and aligned with medical guidelines and standard of care.

Participants who are discontinued from the study drug due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF. Discontinuation of the study drug for abnormal liver tests should be considered by the investigator when a participant meets one of the following conditions after consultation with the sponsor-designated medical monitor:

- ALT or AST ≥8 times ULN
- ALT or AST ≥5 times ULN for more than 2 weeks
- ALT or AST ≥3 times ULN and TBL ≥2 times ULN or international normalized ratio (INR) ≥1.5
- ALT or AST ≥3 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, and/or rash
- ALP ≥3 times ULN
- ALP ≥2.5 times ULN and TBL ≥2 times ULN, or
- ALP ≥2.5 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, and/or rash

Patients who discontinue study drug permanently during study participation must be scheduled for an Early Termination visit.

8.5. Data Safety Monitoring Board

An independent data safety monitoring board (DSMB) comprised of members who are independent of the study sponsor and study investigators will monitor patient safety by conducting formal reviews of accumulated safety data that is blinded by treatment group; if requested, the DSMB may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment.

The DSMB will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study. The DSMB will also institute any measures that may be required for ensuring the integrity of the study results during the study execution.

All activities and responsibilities of the DSMB are described in the DRM06 DSMB charter.

9. STATISTICAL CONSIDERATIONS

9.1. General Statistical Methodology

All statistical processing will be performed using SAS® unless otherwise stated. This study is a blinded study until the parent studies have had database lock and dosing for those studies is no longer blinded. An unblinded interim will be performed to support regulatory submissions when the parent studies have completed the treatment periods. Additional interim analyses may also be performed for regulatory interactions, safety updates, and disclosures.

Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of patients in each category will be presented. For continuous parameters, descriptive statistics will include n (number of patients), mean, standard deviation, median, minimum and maximum.

The Pruritus-NRS weekly mean will be calculated as follows: The mean of each patient's baseline and post-baseline Pruritus-NRS scores will be computed for each week based on the previous 7 days. The weekly mean will be calculated if a patient has responses for Pruritus-NRS on at least 4 of the 7 days of the week. If the patient has 3 or fewer Pruritus-NRS responses, the mean value for that item will be considered missing. All Pruritus-NRS efficacy endpoint analyses will be conducted on the weekly mean.

All safety data from this study will be used as part of integrated summaries, combining with data from the parent studies. For the purposes of the CSR for Study DRM06-AD07, a listing and summary of SAEs and AEs leading to permanent discontinuation of study drug will be created.

Demographic data will be summarized by treatment group using descriptive statistics.

The number of patients in each analysis set will be summarized. Reasons for study withdrawal and treatment withdrawal during the study will be summarized using frequencies and percentages by treatment group.

A statistical analysis plan, describing all statistical analyses will be provided as a separate document.

9.1.1. Populations Analyzed

All entered patients are those who have signed informed consent. This population will be used for tables and/or listings of disposition that include screen failures and inclusion or exclusion criteria.

The ITT population consists of all patients assigned to treatment, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. The modified ITT (mITT) population is the ITT population excluding all patients from sites with critical GCP noncompliance findings related to participant eligibility. mITT population will be used to summarize patient disposition, demographics, and efficacy analyses, plus to list patient data.

All patients who receive at least one confirmed dose of lebrikizumab will be included in the Safety Population. The modified Safety (mSafety) population is the Safety population excluding all patients from sites with critical GCP noncompliance findings related to participant eligibility. Demographics, extent of exposure, treatment compliance, prior or concomitant medication use, adverse event, and immunogenicity safety analyses will be performed using the mSafety Population. A sub-group analysis of safety in patients under 18 years of age (adolescents) will be conducted as appropriate.

The number of patients included in the mSafety population will be summarized.

9.1.2. Baseline Definition

The baseline used for efficacy and immunogenicity endpoints is the parent study baseline.

9.2. EFFICACY ASSESSMENTS

The following efficacy assessments will be summarized at each visit, compared to parent study baseline:

- Proportion of patients with Investigator's Global Assessment (IGA) score = 0 or 1 at each visit
- Proportion of patients with Eczema Area and Severity Index (EASI)-75 (≥75% reduction in EASI scores) at each visit
- Change and percent change in EASI score at each visit
- Proportion of patients with EASI-50 and EASI-90 scores at each visit
- Percentage of patients who achieve a ≥4-point reduction in the Pruritus NRS score at prespecified time points (for studies in which these data were collected)
- Percentage change in Pruritus NRS score at prespecified time points (for studies in which these data were collected)
- Percentage change in Skin Pain NRS score at prespecified time points (for studies in which these data were collected)
- Change in sleep-loss at prespecified time points (for studies in which these data were collected)
- Change in POEM scores at prespecified time points through the end of study (for studies in which these data were collected)
- Change in BSA at prespecified time points through the end of study
- Proportion of patients requiring AD concomitant treatment

9.3. Exposure and Compliance

Exposure to lebrikizumab from the patient's parent study and from study KGAA will be combined for reporting the extent of exposure. The extent of exposure to study drug in each treatment group will be summarized by total number of days of exposure, total number of injections, number of missed injections, and study drug total dose.

The number and percentage of patients who are compliant will be summarized. The treatment compliance calculation is defined as the percentage of the total number of injections administered out of the expected number of injections. A patient will be considered compliant with the dosing regimen if the patient received ≥75% of the expected number of injections while enrolled in the study.

9.4. Adverse Events

The primary endpoint of study DRM06-AD07 is the proportion of patients discontinued from study treatment due to adverse events through the last treatment visit. This proportion will be calculated on the Safety Population from Day 1 to Week 100. For interim analysis, the calculation will be based on all data before interim DBL.

All AEs occurring during the study will be recorded and coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

SAEs and AEs leading to permanent discontinuation of study drug will be summarized by system organ class and preferred term in the Safety Population. All SAEs as well as AEs that led to permanent discontinuation of study drug will be listed by patient.

The data from all studies will be pooled by treatment, 250 mg lebrikizumab Q2W, 250 mg lebrikizumab Q4W, and 250 mg lebrikizumab overall.

The AE data from this study will also be used as part of integrated safety assessments and ongoing safety review through study end.

9.5. Other Safety Data

The vital signs and laboratory data from this study will be used as part of integrated safety assessments and ongoing safety review through study end.

Medical histories will be coded using the MedDRA dictionary and presented in a by-patient listing. Concomitant medications will be coded using the World Health Organization Drug dictionary. Concomitant medications will be summarized by treatment, drug class, and preferred term. Physical examination data will be presented in a by-patient listing.

9.6. Sample-Size Determination

Sample size is based on the number of patients who completed studies DRM06-AD04, DRM06-AD05, DRM06-AD06, DRM06-AD17, and DRM06-AD18 who choose to participate in the study who meet all inclusion and exclusion criteria. It is estimated that approximately 900 patients may enroll from the parent studies.

9.7. Pharmacokinetics Analysis

Plasma concentration data will be tabulated and summarized, such as geometric mean, arithmetic mean, minimum, maximum, SD, and coefficient of variation, by treatment group for each visit at which samples were taken.

It is intended that data from this study will be combined with data from other studies to better characterize the PK of lebrikizumab, as well as to explore the relationship between exposure and efficacy and/or safety outcomes. Further details on PK and PK/PD analyses will be provided in the PK/PD analysis plan. The results of these analyses will be described in a separate PK/PD report.

10. ADMINISTRATION

10.1. Compliance with the Protocol

The study shall be conducted as described in this protocol. All revisions to the protocol must be prepared by the Sponsor. The Investigator will not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study patients. Any significant deviation must be documented and submitted to the IRB/IEC, the Sponsor or designee, and, if required, Regulatory Authority(ies). Documentation of approval signed by the chairperson or designee of the IRB(s)/EC(s) must be sent to the Sponsor and/or designee.

10.2. Informed Consent Procedures

The Informed Consent Form (ICF) will include all elements required by ICH/GCP and applicable regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form will also include a statement that the Sponsor and regulatory authorities have direct access to patient records.

Prior to the beginning of the study, the Investigator will have the IRB/IEC's written opinion (approval/favorable) of the written informed consent form and any other information to be provided to the patients.

The Investigator must provide the patient or legally acceptable representative with a copy of the consent form and written information about the study in the language in which the patient is most proficient. The language must be non-technical and easily understood. The Investigator should allow time necessary for patient or patient's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the patient or the patient's legally acceptable representative, by the Investigator and/or by the person who conducted the informed consent discussion. The patient or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study patients prior to patient's participation in the study.

For patients considered to be minors according to the national legislation in each country, the written consent of the parent or legal guardian must be obtained, as well as the assent of the minor according to his or her capacity to understand the information provided. Patients enrolled as minors who attain legal adulthood during the course of the study must consent in their own right at that time in order to continue participating.

The informed consent and any other information provided to patients or the patient's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the patient's consent, and should receive IRB/IEC approval/ favorable opinion prior to use. The Investigator, or a person designated by the Investigator should fully inform the patient or the patient's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the patient's willingness to continue participation in the study. This communication to the patient should be documented in the source note.

During a patient's participation in the study, any updates to the consent form or to the written information will be provided to the patient in writing.

10.3. Data Protection and Confidentiality

Study patients must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.

Patients must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The Sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.4. Study Documentation and the eCRF

This protocol is to be signed by the investigator responsible for the conduct of this study at the study site. A copy of the signed protocol signature page is to be provided to the Sponsor and retained in the study site's Regulatory Binder.

The Investigator is responsible for ensuring that all study data is accurately recorded on the eCRFs or other study data collection tools. All eCRF entries must be supported by the patient's medical records or source notes. The Investigator must ensure that study observations and findings are legible and recorded accurately and completely.

Original reports, traces and films must be reviewed, signed and dated, and retained by the Investigator for future reference.

The Investigator is expected to promptly review all study data recorded in the patient's source records. Completed eCRFs must be promptly reviewed, signed, and dated by the Investigator or Sub-Investigator at the end of the study. Corrections to data entered into the eCRF will be handled through an electronic query. Corrections to patients' medical or source records should be legible, initialed and dated. At the end of the study, an electronic copy of the investigator's eCRFs will be provided to the Investigator. The Investigator is to retain this data. The Investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on eCRFs. Refer to Section 10.6 regarding retention requirements.

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation for each patient treated with the study drug or entered as a control in the investigation. Data reported on the eCRFs that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

10.5. Study Monitoring

The Sponsor or designee will be responsible for the monitoring of the study. Study monitors will contact and visit the Investigators at regular intervals throughout the study to verify adherence to the protocol, and assess the completeness, consistency, and accuracy of the data by comparing patients' medical records with entries in the eCRF.

The study monitor must be allowed access to laboratory test reports and other patient records needed to verify the entries on the eCRF, provided patient confidentiality is maintained in accordance with local requirements. These records, and other relevant data, may also be reviewed by appropriate qualified personnel independent from the Sponsor or designee, who is appointed to audit the study. Patient confidentiality will be maintained at all times.

By agreeing to participate in this research study, the Investigators agree to co-operate with the study monitor to ensure that any problems detected during the monitoring visits are promptly resolved.

10.6. Retention of Study Documentation

The Investigator must retain study drug disposition records, copies of CRFs and all study-related source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, or for the period specified by the Sponsor, whichever is longer. The Investigator must contact the Sponsor prior to destroying any records associated with the study.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another Investigator, IRB). Notice of such transfer will be given in writing to the Sponsor or designee.

If the Investigator cannot guarantee this archiving requirement for any or all the documents at the investigational site, arrangements must be made between the Investigator and the Sponsor to store these in a secure archive facility outside the site so they can be returned to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

10.7. Publication Policy

In accordance with the sponsor's publication policy the results of this study will be submitted for publication by a peer-reviewed journal.

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12. APPENDICES

APPENDIX 1. SCHEDULE OF VISITS AND PROCEDURES

Table 2: Schedule of Visits and Procedures: Baseline Through End of Study

Study Procedure												
Week (W)	**Baseline[1]**	**W2**	**W4**	**W16**	**W28**	**W40**	**W52**	**W64**	**W76**	**W88**	**W100/ ET**	**12W Post-Dose**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12
Visit Window	-	±3d	±3d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d
Enrollment												
Informed Consent/Assent	X											
Inclusion/Exclusion Criteria	X											
Safety												
Physical Exam	X						X				X	
Height and Weight	X			X[6]	X[6]	X[6]	X[6]		X[6]		X[6]	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications/Procedures	X	X	X	X	X	X	X	X	X	X	X	X
Hematology, Chemistry	X			X	X	X	X		X		X	
HBV DNA[7]	X			X	X	X	X	X	X	X	X	
Estradiol or Testosterone[2]	X			X	X	X	X		X		X	
Urinalysis	X			X		X	X		X		X	
Pregnancy Testing[11]	X	X	X	X	X	X	X	X	X	X	X	
Efficacy												
IGA	X	X	X	X	X	X	X	X	X	X	X	
BSA	X	X	X	X	X	X	X	X	X	X	X	
EASI	X	X	X	X	X	X	X	X	X	X	X	
eDiary: Pruritus, Sleep-loss, POEM[3]	X	X	X	X	X	X	X					
eDiary: TCS/TCI use[3]	X	X	X	X	X	X	X					
eDiary: Skin Pain NRS[8]	X	X	X	X	X	X	X					
eDiary return (patient to site)[9]							X					
POEM (in office collection only)[3]								X	X	X	X	
PK and Immunogenicity												
Pre-dose PK	X		X		X		X		X		X[10]	X[10]
Pre-dose ADA[4]	X		X		X		X		X		X[10]	X[10]
Study Treatment												

Study Procedure												
Week (W)	**Baseline[1]**	**W2**	**W4**	**W16**	**W28**	**W40**	**W52**	**W64**	**W76**	**W88**	**W100/ ET**	**12W Post-Dose**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12
Visit Window	-	±3d	±3d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d
Study Drug Administration[5]	X	X	X	X	X	X	X	X	X	X		
Dispense Study Drug[5]			X	X	X	X	X	X	X	X		

[1] Baseline procedures are conducted as part of parent study exit visit.
[2] Collect estradiol in adolescent females only and testosterone in adolescent males only. Stop hormone tests when the patient reaches 18 years of age.
[3] Daily pruritus and sleep-loss and weekly/in-office POEM only collected for patients participating in DRM06-AD04, DRM06-AD05, DRM06-AD06, and DRM06-AD18. TCS/TCI data only collected for patients participating in DRM06-AD06. In-office POEM should be completed prior to any other study assessments.
[4] nAB testing conducted for positive treatment-emergent ADA responses. Additional immunogenicity sample collected for any patient experiencing a hypersensitivity reaction during study.
[5] Study drug administered Q2W including those patients on Q4W regimen. Patients instructed on study drug administration for at home dosing following Week 4. Sufficient drug is dispensed to cover injections through next visit.
[6] Collect height in adolescents only at these visits. Collect weight in all patients.
[7] Only for participants who are anti-HBc reactive and anti-HBs nonreactive at screening (Section 8.2.3).
[8] Daily Skin Pain NRS only collected for patients participating in DRM06-AD18.
[9] Collect eDiary from patients participating in DRM06-AD04, DRM06-AD05, DRM06-AD06, and DRM06-AD18.
[10] PK and ADA are random collections at Week 100 and the Safety Follow-up.
[11] Urine pregnancy tests for women of childbearing potential (Section 8.2.3).

APPENDIX 2. LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Hepatic evaluation testing
See Section 8.2.3 for guidance on appropriate test selection.
The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.
Local testing may be performed in addition to central testing when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin-time/International normalized ratio(PT-INR)	Haptoglobin
Serology	Immunoglobulin A (IgA; quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin G (IgG; quantitative)
HAV total antibody	Immunoglobulin M (IgM; quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatitis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)

Hematology	**Clinical Chemistry**
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA)[a]
HBV DNA[d]	Anti-actin antibody[b]
Hepatitis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA[d]	EBV DNA[d]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[d]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[d]	HSV (Type 1 and 2) DNA[d]
Microbiology[c]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

a Not required if anti-actin antibody is tested.
b Not required if ASMA is tested.
c Assayed ONLY by investigator-designated local laboratory; no central testing available.
d Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

APPENDIX 3. PROTOCOL AMENDMENT (1) HISTORY

The table below summarizes new changes being introduced to Amendment 1. Minor corrections or additions may not be included.

Protocol Section	Description of Change	Rationale
Title Page Sponsor Signature Page	Updated medical monitor and contact information	Change in personnel
Protocol Synopsis 3 Study Design 3.1 Duration of the Study	Added 48 weeks of treatment	To gain additional safety data on long-term exposures
Protocol Synopsis 3 Study Design 4.1 Inclusion Criteria	Modified Study Design and inclusion criterion 1: "…in a Dermira- or Lilly-sponsored lebrikizumab study…"	Correction
Protocol Synopsis 3 Study Design 5.3 Study Drug Assignment	Added text for the monotherapy trials, AD04 and AD05, "…until unblinding (see Section 5.4), except for patients from an escape arm, who will receive open-label study drug"	Clarification
Protocol Synopsis 3 Study Design 5.3 Study Drug Assignment	Added language describing the treatment assignment for patients who received rescue treatment in DRM06-AD06 Added language to clarify blinding plan for patients from DRM06-AD06	Clarification
Protocol Synopsis 3 Study Design 5.3 Study Drug Assignment	Clarified treatment group for patients coming from DRM06-AD17 and the escape arm (DRM06-AD04 and DRM06-AD05), "…will continue to receive open label 250 mg…"	Clarification
Protocol Synopsis 3 Study Design	"Patients not achieving an EASI-50 (from parent study baseline) by Week 16, ~~or~~ maintaining an EASI-50 response, or not achieving clinical benefit based on PI discretion should be terminated from this study"	Clarification

Protocol Section	Description of Change	Rationale
Protocol Synopsis	Modified language on interim analyses: "An unblinded interim analysis will be performed to support regulatory submissions ~~when the parent studies have completed the treatment periods~~"	Need to maintain blinding up to regulatory submission
1.3.1.3 Summary of Dose Ranging Study DRM06-AD01	Updated safety results	Update
4.1 Inclusion Criteria	Updated contraception requirements (criterion 3)	Female language added as clarification for allowable contraceptive methods
4.1 Inclusion Criteria	Removed male contraception requirements (criterion 4)	Male language modifications supported by available toxicology data
5.4 Study Blinding	"For trials where blinding to treatment will be maintained, the Investigator, study-site personnel, and the patient will be blinded to treatment assignment until ~~the parent studies have had database lock and dosing for those studies are no longer blinded~~ the unblinded interim analysis to support regulatory submissions occurs" Added "After the interim database lock for the submission, patients will no longer receive placebo injections and will continue per assigned treatment group"	Clarification of study drug administration after unblinding
5.5.2 Instructions for Administration at Home	Updated how patients will receive instructions for use	Correction
6.3 Treatments for AD	Modified example language for permitted topical rescue medications: "~~low- and mid-potency~~ TCS, TCI's and PDE4 inhibitors…"	Clarification
7.1 Baseline Visit (Day 1)	"…will be transferred electronically into the	Clarification

Protocol Section	Description of Change	Rationale
	electronic data capture system where possible"	
7 Study Procedures (7.1 through 7.13) Appendix 1 Schedule of Visits and Procedures	Added 48 weeks of treatment (4 additional visits) Added Informed Consent/Assent at Baseline Added HBV DNA Added hematology, chemistry, and urinalysis to additional visits Added dosing diary through Week 100 Added Skin Pain NRS for patients continuing from DRM06-AD18, through Week 52	To obtain additional long-term safety data Informed Consent/Assent added for clarification
8.1.4 Pruritus 8.1.5 Sleep-Loss	"Assessments will be recorded daily by the patient using an electronic diary through Week 52"	Reduce patient burden for additional 48 weeks added
8.1.6 Patient Oriented Eczema Measure (POEM)	"POEM responses will be captured using an electronic diary through Week 52, then captured at site visits starting at Week 64…"	Reduce patient burden for additional 48 weeks added
8.1.7 Skin Pain Numeric Rating Scale (NRS)	Added subsection	Added for patients continuing from DRM06-AD18
8.2.3 Laboratory Evaluations	Added instructions for clinically significantly abnormal laboratory values and blinding of laboratory test results	Clarification
8.2.7 Hepatic Safety Monitoring	Added section and subsections	To provide detailed guidance for hepatic safety monitoring and hepatitis safety instructions
8.4.1 Early Termination of Study Patients 8.4.2 Discontinuation of Inadvertently Enrolled Patients	Added reasons for which a patient may terminate or be terminated early from the study, including • not achieving clinical benefit • enrollment in another medically	Clarification

Protocol Section	Description of Change	Rationale
	incompatible clinical study • requiring long-term systemic treatment for symptoms of AD (that is, non-responders), and • inadvertent enrollment	
8.4.3 Study Drug Discontinuation 8.4.3.1 Temporary Study Drug Discontinuation 8.4.3.2 Permanent Study Drug Discontinuation	Added subsections	To provide instructions for withholding study drug when warranted for patient safety
9.1 General Statistical Methodology	Added language to describe use of safety data	Clarification
9.1 General Statistical Methodology	"Reasons for study withdrawal and treatment withdrawal during the study will be summarized…"	Clarification
9.1.1 Populations Analyzed	Updated subsection to further describe populations analyzed	Clarification
9.1.2 Baseline Definition	Added subsection	Clarification
9.2 Efficacy Assessments	Added and modified language to clarify how assessments will be performed	Clarification
9.3 Exposure and Compliance	Added and modified language to clarify extent of exposure reporting and treatment compliance definition	Clarification
9.4 Adverse Events	Added language describing the primary endpoint and how SAEs and AEs will be analyzed	Clarification
9.5 Other Safety Data	Modified description of vital signs and laboratory data	Details will be provided in the SAP
9.6 Sample-Size Determination	Added estimate for sample size	Clarification
9.7 Pharmacokinetics Analysis	Added section	To provide details on PK analysis
Appendix 2 Liver Safety: Suggested Actions and Follow-up Assessments	Added appendix	To provide detailed guidance for liver safety actions and follow-up information

Protocol Section	Description of Change	Rationale
Throughout protocol	Added DRM06-AD18 as parent study	Clarification

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